REMARKS

Claims 6-9 and 11-31are pending. As discussed, independent Claims 6 and 18 have now been limited to isolated chlorogenic acid compounds for component (A). New Claims 19 and 20, which are directed to stereoisomers of chlorogenic acid, find support in the specification on page 6, lines 7-10. Support for Claims 21-29, which are directed to specific types of chlorogenic acid, is found on page 6, lines 10-18, which defines the term chlorogenic acid. (For the Examiner's convenience, copies of pages from the Merck Index (1996) describing the structures of chlorogenic acid, caffeic acid, ferulic acid and quinic acid are attached.) Claims 30 and 31, which specifically refer to acetic acid and lactic acid, find support in the specification at page 12, line 4.

The Applicants thank Examiner Coe for the courteous and helpful interview of June 16, 2003. The Examiner indicated that claims directed to methods of treating hypertension using chlorogenic acid and an organic acid would likely be allowable. Such methods were previously indicated as being free of the prior art. As discussed, the claims have now been so directed. The Applicants submit that new Claims 19-31 do not raise new issues as these claims depend from allowable Claim 6 and merely refer to particular subtypes of chlorogenic acid or organic acids that are already encompassed by the independent claim. Favorable consideration for these claims is respectfully requested.

Election/Restriction

In view of the limitation of the claims to methods involving isolated chlorogenic acid, the Applicants respectfully request rejoinder of Claims 8, 11-14 and 16-18, as these claims are also directed to methods involving treatment of hypertension using isolated chlorogenic acid.

Claim Objections

Claim 10 was objected to as not further limiting the subject matter of Claim 6. This objection is moot in view of the cancellation of Claim 10.

Rejection—35 U.S.C. 103

Claims 6, 9, 10 and 15 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Japanese Patent Application No. 04243822 and Ahn, U.S. Patent No. 4,981,852. This rejection is moot in view of the limitation of the claims to methods involving isolated chlorogenic acid. The cited prior art does not disclose or suggest the claimed methods. JP '822 (English abstract) is directed to calcium antagonists, but does not disclose or suggest methods involving isolated chlorogenic acid. Ahn is directed to a triamterene and hydrochlorothiazides and does not disclose or suggest methods involving isolated chlorogenic acid.

CONCLUSION

In view of the above amendments and remarks, the Applicants respectfully submit that this application is now in condition for allowance. Early notification to that effect is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Norman F. Oblon
Attorney of Record
Registration No. 24,618

Thomas M. Cunningham
Registration No. 45,394

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(703) 413-3000
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to moist air. Practically insol in water and acids, except nitric, in which it is sol with decompn.

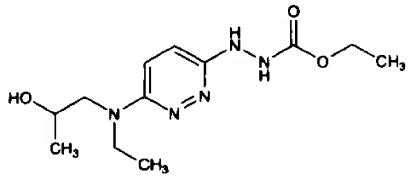
USE: In semiconductor research, in phosphors.

1668. Cadmium Tungstate(VI). CdO_4W; mol wt 360.25. Cd 31.20%, O 17.76%, W 51.03%. $CdWO_4$. Prepn: Karl, *Compt. Rend.* **196,** 1403 (1933); prepn of single crystals: Uitert, Soden, *J. Appl. Phys.* **31,** 328 (1960).

White or yellowish monoclinic crystals or powder. Practically insol in water or dil acids. Sol in solns of alkali cyanides.

USE: In x-ray screens; in scintillation counters; in phosphors; as catalyst for organic reactions.

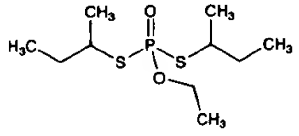
1669. Cadralazine. *2-[6-[Ethyl(2-hydroxypropyl)amino]-3-pyridazinyl]hydrazinecarboxylic acid ethyl ester;* ethyl 6-[ethyl(2-hydroxypropyl)amino]-3-pyridazinecarbazate; 3-(2-carbethoxyhydrazino)-6-[*N*-(2-hydroxypropyl)ethylamino]pyridazine; DC-826; ISF-2469; Cadral; Cadraten; Cadrilan; Presmode. $C_{12}H_{21}N_5O_3$; mol wt 283.33. C 50.87%, H 7.47%, N 24.72%, O 16.94%. Peripheral vasodilator similar to hydralazine, *q.v.* Prepn: C. Carpi *et al.*, **Belg. pat. 811,847;** *eidem,* **U.S. pats. 3,925,381; 4,002,753** (1974, 1975, 1977 all to ISF); F. Parravicini *et al., Farmaco Ed. Sci.* **34,** 299 (1979). Analytical profile: L. Citerio *et al., Boll. Chim. Farm.* **120,** 222 (1981). Pharmacology: C. Semeraro *et al., J. Cardiovasc. Pharmacol.* **3,** 455 (1981). HPLC determn in plasma and urine: T. Crolla *et al., J. Chromatog.* **310,** 139 (1984). Hemodynamic effects in dogs: L. Dorigotti *et al., Arzneimittel-Forsch.* **34,** 984 (1984); in humans: B. Persson *et al., Eur. J. Clin. Pharmacol.* **31,** 513 (1987). Pharmacokinetics and metabolism in humans: H. Schütz *et al., Eur. J. Drug Metab. Pharmacokinet.* **10,** 147 (1985); S. A. Hauffe *et al., ibid.* 217. Preliminary clinical evaluations: R. Buoninconti, M. Motolese, *Int. J. Clin. Pharmacol. Ther. Toxicol.* **23,** 613 (1985); A. Salvadeo *et al., Arzneimittel-Forsch.* **35,** 623 (1985).



Crystals from acetone, mp 160-162°. pKa 6.0. uv max: 248, 340 nm (ε 22100, 2250). Soly (mg/ml): water 1.3; HCl 235.0; DMSO 323.0; methanol 21.0; dioxane 18.6; chloroform 8.5; diethyl ether, benzene, cyclohexane < 0.1. LD_{50} in rats, dogs (mg/kg): 269, approx 400 i.v.; 2060, > 2000 orally (Semeraro); in mice (mg/kg): 700 i.p. (Parravicini).

THERAP CAT: Antihypertensive.

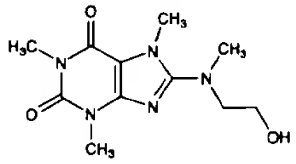
1670. Cadusafos. *Phosphorodithioic acid O-ethyl S,S-bis(1-methylpropyl) ester; S,S*-di-*sec*-butyl *O*-ethyl phosphorodithioate; ebufos; FMC-67825; Apache; Rugby; Taredan. $C_{10}H_{23}O_2PS_2$; mol wt 270.40. C 44.42%, H 8.57%, O 11.83%, P 11.45%, S 23.72%. Organophosphate insecticide structurally similar to ethoprop, *q.v.* Manufacturing process: J. M. Brochard *et al.*, Eur. pat. **Appl. 235,056** (1987 to Rhone-Poulenc Agrochimie). Field trial as nematocide for bananas: P. Quénéhervé *et al., Rev. Nematol.* **14,** 251 (1991). Behavior in soils: S. Q. Zheng *et al., Sci. Total Environ.* **156,** 1 (1994).



Colorless to yellow liquid. Vapor press (25°): 120 mPa. Soly in water: 248 mg/l.

USE: Insecticide; nematocide.

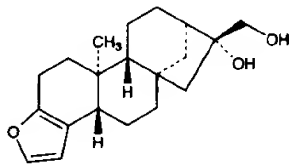
1671. Cafaminol. *3,7-Dihydro-8-[(2-hydroxyethyl)methylamino]-1,3,7-trimethyl-1H-purine-2,6-dione; 8-[(2-hydroxyethyl)methylamino]caffeine;* 8-(β-oxyethyl)methylaminocaffeine; methylcoffanolamine; Rhinoptil. $C_{11}H_{17}N_5O_3$; mol wt 267.29. C 49.43%, H 6.41%, N 26.20%, O 17.96%. Alkanolamine deriv of caffeine, *q.v.* Prepn: J. Klosa, **Ger. pat. 1,085,530;** *eidem,* **U.S. pat. 3,094,531** (1958, 1963 both to Delmar Chemicals Ltd.). Efficacy studies: E. Szirmai, *Praxis* **13,** 412 (1969); R. Leypoldt, *Therapiewoche* **26,** 3381 (1976). Bioavailability and absorption kinetics in humans: H. Walther, K. Kochler, *Pharmazie* **34,** 375 (1979).



Colorless crystals from ethanol, mp 162-164°. Soly in water is about 6%; pH of aq solns is 6.9. LD_{50} s.c. in male mice: 700 mg/kg (Klosa).

THERAP CAT: Decongestant (nasal).

1672. Cafestol. *[3bS-(3bα,5aβ,7β,8β,10aα,10bβ)]-3b,4,5,6,7,8,9,10,10a,10b,11,12-Dodecahydro-7-hydroxy-10b-methyl-5a,8-methano-5aH-cyclohepta[5,6]naphtho[2,1-b]furan-7-methanol;* cafesterol. $C_{20}H_{28}O_3$; mol wt 316.44. C 75.91%, H 8.92%, O 15.17%. Diterpenoid constituent of coffee. Isoln from green coffee oil: Slotta, Neisser, *Ber.* **71,** 1991, 2342 (1938); C. Djerassi *et al., J. Org. Chem.* **18,** 1449 (1953). Prepn and purification: R. Bertholet, U.S. pat. **4,692,534** (1987 to Nestec). Structure: C. Djerassi *et al., J. Am. Chem. Soc.* **81,** 2386 (1959); R. A. Finnegan, C. Djerassi, *ibid.* **82,** 4342 (1960). Stereochemical studies: R. A. Finnegan, *J. Org. Chem.* **26,** 3057 (1961); A. I. Scott *et al., J. Am. Chem. Soc.* **84,** 3197 (1962); A. I. Scott *et al., Tetrahedron* **20,** 1339 (1964). Stereospecific total synthesis of (±)-form: E. J. Corey *et al., J. Am. Chem. Soc.* **109,** 4717 (1987).

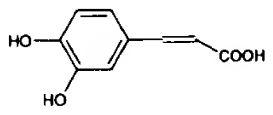


Crystals from hexane, mp 158-160°. $[\alpha]_D$ −101°. uv max: 222 nm (log ε 3.78).

Acetate, $C_{22}H_{30}O_4$, needles from petr ether, mp 167-168°. $[\alpha]_D$ −89°. uv max: 222 nm (log ε 3.80).

Tetrahydrocafestol, $C_{20}H_{32}O_3$, crystals from dil methanol, mp 154.5-157°.

1673. Caffeic Acid. *3-(3,4-Dihydroxyphenyl)-2-propenoic acid; 3,4-dihydroxycinnamic acid.* $C_9H_8O_4$; mol wt 180.16. C 60.00%, H 4.48%, O 35.52%. Constituent of plants, probably occurs in plants only in conjugated forms, e.g., chlorogenic acid. Isoln from green coffee: Wolfrom *et al., J. Agr. Food Chem.* **8,** 58 (1960); from roasted coffee: Krasemann, *Arch. Pharm.* **293,** 721 (1960). Formation by acid hydrolysis of chlorogenic acid: Fiedler, *Arzneimittel-Forsch.* **4,** 41 (1954); Whiting, Carr, *Nature* **180,** 1479 (1957); Guern, *C.A.* **61,** 9965h (1964). Synthesis: Hayduck, *Ber.* **36,** 2935 (1903); Posner, *J. Prakt. Chem.* **82,** 432 (1910); Mauthner, *ibid.* **142,** 33 (1935); Pandya *et al., Proc. Indian Acad. Sci.* **9A,** 511 (1939); Neish, *Can. J. Biochem. Physiol.* **37,** 1431 (1959). *Review:* Herrmann, *Pharmazie* **11,** 433 (1956).

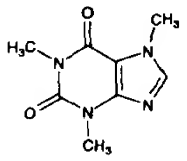


Yellow crystals from concd aq solns. Monohydrate from dil solns. Dec 223-225° (softens at 194°). R_f values: Fied-

ler, *loc. cit.* Sparingly sol in cold water. Freely sol in hot water, cold alc. Alkaline solns turn from yellow to orange.

Methyl ester, $C_{10}H_{10}O_4$, colorless needles from water, mp 152-153°.

1674. Caffeine. *3,7-Dihydro-1,3,7-trimethyl-1H-purine-2,6-dione;* 1,3,7-trimethylxanthine; 1,3,7-trimethyl-2,6-dioxopurine; coffeine; thein; guaranine; methyltheobromine; No-Doz. $C_8H_{10}N_4O_2$; mol wt 194.19. C 49.48%, H 5.19%, N 28.85%, O 16.48%. Occurs in tea, coffee, maté leaves; also in guarana paste and cola nuts: Shuman, U.S. pat. **2,508,545** (1950 to General Foods). Obtained as a by-product from the manuf of caffeine-free coffee: Barch, U.S. pat. **2,817,588** (1957 to Standard Brands); Nutting, U.S. pat. **2,802,739** (1957 to Hill Bros. Coffee); Adler, Earle, U.S. pat. **2,933,395** (1960 to General Foods). Crystal structure: Sutor, *Acta Cryst.* **11,** 453 (1958). Synthesis: Fischer, Ach, *Ber.* **28,** 2473, 3135 (1895); Gepner, Kreps, *J. Gen. Chem. USSR* **16,** 179 (1946); Bredereck *et al., Ber.* **83,** 201 (1950); Crippa, Crippa, *Farmaco Ed. Sci.* **10,** 616 (1955); Swidinsky, Baizer, U.S. pats. **2,785,162** and **2,785,163** (1957 to Quinine Chem. Works); Bredereck, Gotsmann, *Ber.* **95,** 1902 (1962). Reversed-phase HPLC study: J. W. Weyland *et al., J. Chromatog.* **247,** 221 (1982). Effect of pregnancy on the pharmacokinetics of caffeine: R. Knutti *et al., Arch. Toxicol.* **5,** Suppl., 187 (1982). Binding of caffeine on benzodiazepine receptors: V. Saano, M. M. Airaksinen, *Acta Pharmacol. Toxicol.* **51,** 300 (1982). Disposition of caffeine and its metabolites in man: D. D. Tang-Liu *et al., J. Pharmacol. Exp. Ther.* **224,** 180 (1983). Arrhythmogenic effects in humans: D. J. Dobmeyer *et al., N. Engl. J. Med.* **308,** 814 (1983). Teratogenicity study: P. E. Palm *et al., Toxicol. Appl. Pharmacol.* **44,** 1 (1978). Comprehensive description: M. U. Zubair *et al.* in *Analytical Profiles of Drug Substances* **vol. 15,** K. Florey, Ed. (Academic Press, New York, 1986) pp 71-150.



Hexagonal prisms by sublimation, mp 238°. Sublimes 178°. Fast sublimation is obtained at 160-165° under 1 mm press. at 5 mm distance. d_4^{18} 1.23. pH of 1% soln 6.9. Aq solns of caffeine salts dissociate quickly. Absorption spectrum: Hartley, *J. Chem. Soc.* **87,** 1802 (1905). One gram dissolves in 46 ml water, 5.5 ml water at 80°, 1.5 ml boiling water, 66 ml alcohol, 22 ml alcohol at 60°, 50 ml acetone, 5.5 ml chloroform, 530 ml ether, 100 ml benzene, 22 ml boiling benzene. Freely sol in pyrrole; in tetrahydrofuran contg about 4% water; also sol in ethyl acetate; slightly in petr ether. Soly in water is increased by alkali benzoates, cinnamates, citrates or salicylates. LD_{50} orally in mice, hamsters, rats, rabbits (mg/kg): 127, 230, 355, 246 (males); 137, 249, 247, 224 (females) (Palm).

Monohydrate, felted needles, contg 8.5% H_2O. Efflorescent in air; complete dehydration takes place at 80°.

Hydrochloride dihydrate, $C_8H_{11}ClN_4O_2 \cdot 2H_2O$, crystals, dec 80-100° with loss of water and HCl. Sol in water and in alcohol with dec.

Mixture with citric acid, *citrated caffeine, "caffeine citrate".* White, crystalline powder; acid reaction. Sol in about 4 parts warm water.

THERAP CAT: CNS stimulant.

THERAP CAT (VET): Has been used as a cardiac and respiratory stimulant and as a diuretic.

1675. Calamine. Eczederm. Prepd calamine. Zinc oxide with about 0.5% ferric oxide.

Pink powder. Insol in water. Almost completely sol in mineral acids.

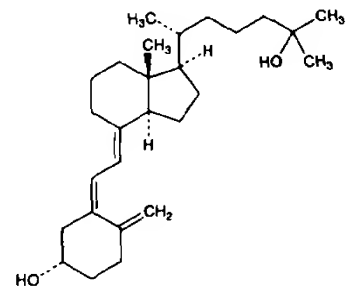
THERAP CAT: Topical protectant.

THERAP CAT (VET): Astringent. Skin protectant.

1676. Calamus. Sweet flag; calmus; sweet cane; sweet grass. Dried rhizome of *Acorus calamus* L., *Araceae. Habit.* Europe, North America, Western Asia; cultivated in Burma and Ceylon. *Constit.* Acorin, acoretin (choline), 1.5% volatile oil, 2.5% resins, 1.5% tannins; also reducing sugars and sterol bodies. *Ref:* Bose *et al., J. Am. Pharm. Assoc.* **49,** 32 (1960).

THERAP CAT: Carminative, anthelmintic.

1677. Calcifediol. *(3β,5Z,7E)-9,10-Secocholesta-5,7,10(19)-triene-3,25-diol;* 25-hydroxyvitamin D_3; 25-hydroxycholecalciferol; 25-HCC; U-32070E; Calderol; Dedrogyl; Didrogyl; Hidroferol. $C_{27}H_{44}O_2$; mol wt 400.65. C 80.94%, H 11.07%, O 7.99%. The principal circulating form of vitamin D_3, formed in the liver by hydroxylation at C-25: Ponchon, DeLuca, *J. Clin. Invest.* **48,** 1273 (1969). It is the intermediate in the formation of 1α,25-dihydroxycholecalciferol, *q.v.*, the biologically active form of vitamin D_3 in the intestine. Identification in rat as an active metabolite of vitamin D_3: Lund, DeLuca, *J. Lipid Res.* **7,** 739 (1966); Morii *et al., Arch. Biochem. Biophys.* **120,** 513 (1967). Evaluation of biological activity in comparison with vitamin D_3: Blunt *et al., Proc. Nat. Acad. Sci. USA* **61,** 717 (1968); *ibid.* 1503. Isoln from porcine plasma and establishment of structure: Blunt *et al., Biochemistry* **7,** 3317 (1968). Synthesis: Blunt, DeLuca, *ibid.* **8,** 671 (1969). Review of isoln, identification and synthesis: DeLuca, *Am. J. Clin. Nutr.* **22,** 412 (1969). Review of bioassays: J. G. Haddad Jr., *Basic Clin. Nutr.* **2,** 579-597 (1980).



uv max (ethanol): 265 nm (ε 18000) (Blunt, DeLuca).

THERAP CAT: Calcium regulator.

1678. Calcimycin. *6S-[6α(2S*,3S*),8β(R*),9β,11α]-5-(Methylamino)-2-[[3,9,11-trimethyl-8-[1-methyl-2-oxo-2-(1H-pyrrol-2-yl)ethyl]-1,7-dioxaspiro[5.5]undec-2-yl]methyl]-4-benzoxazolecarboxylic acid;* antibiotic A-23187; A-23187. $C_{29}H_{37}N_3O_6$; mol wt 523.63. C 66.52%, H 7.12%, N 8.02%, O 18.33%. Polyether antibiotic produced by a strain of *Streptomyces chartreusensis* Calhoun and Johnson NRRL 3882. Activity as a divalent cation ionophore in isolated mitochondria: P. W. Reed, H. A. Lardy, *J. Biol. Chem.* **247,** 6970 (1972). Prepn and antimicrobial activity: R. M. Gale *et al.,* U.S. pat. **3,923,823** (1975 to Lilly). Elucidation of structure: M. O. Chaney *et al., J. Am. Chem. Soc.* **96,** 1932 (1974). Spectral studies of ionophore and metal ion complexes: D. R. Pfeiffer *et al., Biochemistry* **13,** 4007 (1974). Total synthesis and absolute configuration: D. A. Evans *et al., J. Am. Chem. Soc.* **101,** 6789 (1979); P. A. Grieco *et al., J. Org. Chem.* **45,** 3537 (1980). Stereospecific synthesis: G. R. Martinez *et al., J. Am. Chem. Soc.* **104,** 1436 (1982); D. P. Negri, Y. Kishi, *Tetrahedron Letters* **28,** 1063 (1987). Review of cation binding and transport properties: D. R. Pfeiffer *et al., Ann. N.Y. Acad. Sci.* **307,** 402-423 (1978). Use in model systems of calcium transport: M. Takamori *et al., J. Neurol. Sci.* **50,** 89 (1981); M. Takamori *et al., ibid.* **51,** 207 (1981); M. H. Freedman *et al., Cell. Immunol.* **58,** 134 (1981); G. Thomas, *Eur. J. Pharmacol.* **81,** 35 (1982); V. L. Lew, J. Garcia-Sancho, *Cell Calcium* **6,** 15 (1985).

1460. n_D^{20} 1.4234. Flash pt 53.89°
Chem. **32**, 880 (1940). Practically
hol.
Henderson, U.S. pat. **3,179,506**

)Dibenzylamine Hydrochloride. *(methyl)benzenemethanamine hy-β-chloroethylamine hydrochloride; Di-* $C_{16}H_{19}Cl_2N$; mol wt 296.24. C 64%, N 4.73%. $(C_6H_5CH_2)_2N$-ergic blocker. Prepn: Rabald, 8 (1951 to Boehringer, Mann.), harmacology and toxicity: M. uchi, *J. Pharmacol. Exp. Ther.* renergic receptor differentiation: 265 (1954); in specific receptor *ibid.* **187**, 524 (1973). *In vivo* st hepatotoxic agents: H. M. *Pharmacol.* **27**, 380 (1974); E. 8, 477 (1974); H. M. Maling *et* 1479 (1974).
en as 180-181° (the free base is insol in water near neutrality. , 1% at pH 2.4 and 0.5% at pH ropylene glycol. Stable in acid ty in neutral or alkaline solns. g (Nickerson, Nomaguchi).

yl Ether. *(2-Chloroethoxy)eth-* 55. C 45.09%, H 6.62%, Cl $H_2OCH=CH_2$. Prepd by the hanolamine upon β,β'-dichlo- Perkins, U.S. pat. **2,104,717** Chem.); *cf.* Cretcher *et al., J.* 6). Toxicity study: Smyth *et* 0 (1949).
109°. Quite stable to NaOH e hydrolysis to acetaldehyde hloroethanol]. LD_{50} orally in

ves, cellulose ethers.

s. CFCs; FCCs. Chemically ind fluorinated compounds ne skeleton, marketed under *n, Freon, Frigen, Genetron.* individually identified by a f 90". (To derive the chemi- dd "90" to 12; the resulting on, 0 hydrogen, 2 fluorine nitial report on suitability as L. Henne, *Ind. Eng. Chem.* ding physical and chemical . Heiskel, *Aerosol Rep.* **22**, decompose in the lower at- occurs in the stratosphere and subsequent release of atalyze ozone breakdown. : M. J. Molina, F. S. Row- Reviews focusing on atmo- potential hydrogen-substi- al and regulatory issues: J. 0 (1987); R. Pool, *Science* and, *Environ. Conserv.* **15**, *Plast. Comp.* **1988**, 15-22, *tist* **77**, 36-45 (1989). For ifluoromethane (CFC-12), cryofluorane (CFC-114). nonflammable, noncorro- yclic and aromatic hydro- is, monovalent low molec-

ent regulations on use as

FC-11, 12, 113); air con- blowing agents for mak- luids (CFC-113); solvents ng and packaging.

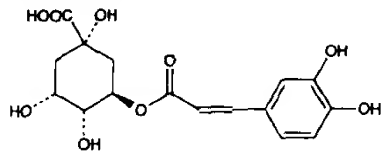
2193. Chloroform. *Trichloromethane.* $CHCl_3$; mol wt 119.38. C 10.06%, H 0.84%, Cl 89.09%. Improperly called "formyl trichloride". Made from acetone and bleaching powder by addition of sulfuric acid: $2CH_3COCH_3 + 6CaOCl_2.H_2O \rightarrow 2CHCl_3 + (CH_3COO)_2Ca + 2Ca(OH)_2 + 3CaCl_2 + 6H_2O$. May also be prepd by carefully controlled chlorination of methane: Faith, Keyes & Clark's *Industrial Chemicals*, F. A. Lowenheim, M. K. Moran, Eds. (Wiley-Interscience, New York, 4th ed., 1975) pp 266-269. Has been used as an anesthetic and in pharmaceutical preparations. Toxicity data: H. F. Smyth *et al., Am. Ind. Hyg. Assoc. J.* **23**, 95 (1962); E. T. Kimura *et al., Toxicol. Appl. Pharmacol.* **19**, 699 (1971). Review of toxicology: L. R. Pohl, *Rev. Biochem. Toxicol.* **1**, 79-108 (1979). Review of carcinogenicity studies: *IARC Monographs* **20**, 401-427 (1979). *Review:* M. T. Holbrook in Kirk-Othmer *Encyclopedia of Chemical Technology* **vol. 5** (John Wiley & Sons, New York, 4th ed., 1993) pp 1051-1062.

Highly refractive, nonflammable, heavy, very volatile, sweet-tasting liquid; characteristic odor. d_{20}^{20} 1.484. bp 61-62°. mp −63.5°. n_D^{20} 1.4476. Forms a constant boiling mixture with 7% alc, boiling at 59°. d 1.474-1.478 for U.S.P. chloroform contg 0.5-1% ethanol as stabilizer. One ml dissolves in about 200 ml water at 25°. Misc with alcohol, benzene, ether, petr ether, carbon tetrachloride, carbon disulfide, oils. Pure chloroform is light sensitive and reagent grade chloroform usually contains 0.75% ethanol as stabilizer. *Protect from light and keep cool.* LD_{50} (14 day) orally in rats: 2.18 ml/kg (Smyth); 0.9 ml/kg (Kimura).

Caution: Potential symptoms of overexposure are dizziness, mental dullness, nausea and disorientation; headache, fatigue; anesthesia; hepatomegaly; direct contact may cause irritation to eyes and skin. *See NIOSH Pocket Guide to Chemical Hazards* (DHHS/NIOSH 90-117, 1990) p 68. Banned from use in foods, drugs and cosmetics by the FDA. This substance may reasonably be anticipated to be a carcinogen: *Seventh Annual Report on Carcinogens* (PB95-109781, 1994) p 127.

USE: As a solvent for fats, oils, rubber, alkaloids, waxes, gutta-percha, resins; as cleansing agent; in fire extinguishers to lower the freezing temp of carbon tetrachloride; in the rubber industry.

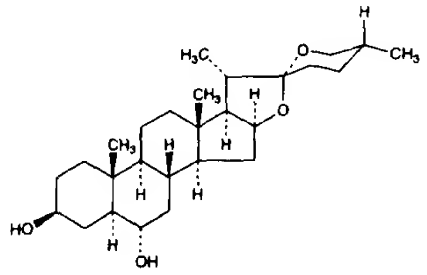
2194. Chlorogenic Acid. *[1S-(1α,3β,4α,5α)]-3-[[3-(3,4-Dihydroxyphenyl)-1-oxo-2-propenyl]oxy]-1,4,5-trihydroxycyclohexanecarboxylic acid; 1,3,4,5-tetrahydroxycyclohexanecarboxylic acid 3-(3,4-dihydroxycinnamate);* 3-caffeoylquinic acid; 3-(3,4-dihydroxycinnamoyl)quinic acid. $C_{16}H_{18}O_9$; mol wt 354.31. C 54.24%, H 5.12%, O 40.64%. Important factor in plant metabolism. Isoln from green coffee beans: Freudenberg, *Ber.* **53**, 237 (1920). Chlorogenic acid and its isomers isochlorogenic acid and neochlorogenic acid occur also in fruit, leaves and other tissues of dicotyledenous plants: Sondheimer, *Arch. Pharm.* **293**, 721 (1960). Forms caffeic acid on hydrolysis: Fiedler, *Arzneimittel-Forsch.* **4**, 41 (1954). Structure: Fischer, Dangschat, *Ber.* **65**, 1037 (1932); Barnes *et al., J. Am. Chem. Soc.* **72**, 4178 (1950); Corse *et al., Tetrahedron* **18**, 1207 (1962). Synthesis: Panizzi *et al., Gazz. Chim. Ital.* **86**, 913 (1956).



Hemihydrate, needles from water. Becomes anhydr at 110°. mp 208°. $[\alpha]_D^{25}$ −35.2° (c = 2.8). pKa (27°) 2.66. R_f values: Fiedler, *loc. cit.* Soly in water at 25° about 4%, much more sol in hot water. Alkaline solns acquire an orange color. Freely sol in alcohol, acetone. Very slightly sol in ethyl acetate. Heating with dil HCl yields caffeic acid. Forms a black compd with iron, said to be responsible for the blackening of cut and cooked potatoes: *Chem. & Ind. (London)* **1958**, 627.

3'-Methyl ether, $C_{17}H_{20}O_9$, *3-feruloylquinic acid.* Crystals from ethyl acetate + petr ether, mp 196-197°. $[\alpha]_D^{15}$ −42.8° (ethanol). uv max (ethanol): 325 nm (ε 19,200).

2195. Chlorogenin. *(3β,5α,6α,25R)-Spirostan-3,6-diol.* $C_{27}H_{44}O_4$; mol wt 432.64. C 74.96%, H 10.25%, O 14.79%. Isoln from bulbs of the California soap plant, amole: *Chlorogalum pomeridianum* (DC.) Kunth, *Liliaceae:* Liang, Noller, *J. Am. Chem. Soc.* **57**, 525 (1935). Chlorogenin occurs in amole as a saponin which kills or stuns fish without rendering them inedible. Structure: Marker, Rohrmann, *ibid.* **61**, 947, 3479 (1939); Marker *et al., ibid.* **62**, 2537, 3006 (1940). On hydrogenation the 3β,6β-isomer (β-chlorogenin) is produced.



Needles from methanol, mp 273-276°. $[\alpha]_{546}^{24}$ −52° (chloroform or isopropanol). Less sol in methanol, more sol in isopropanol than tigogenin.

Diacetate, crystals from dil methanol, mp 154-155°.

Dibenzoate, crystals from methanol + chloroform, mp 200.5-204.5°, $[\alpha]_{546}^{24}$ +9.5° (chloroform).

2196. 1-Chlorohexane. *n*-Hexyl chloride. $C_6H_{13}Cl$; mol wt 120.62. C 59.75%, H 10.86%, Cl 29.39%. $CH_3(CH_2)_4CH_2Cl$. Prepd from 1-hexanol by treatment with fuming HCl: Henry, *Chem. Zentr.* **1905, II**, 214; with excess $SOCl_2$ or with $PCl_5 + ZnCl_2$: Clark, Streight, *Trans. Roy. Soc. Can.* [3] **23, III**, 77 (1929).

Mobile liquid. d_4^{20} 0.8780. bp_{760} 134°. n_D^{20} 1.4236 (Clark, Streight, *loc. cit.*); n_D^{20} 1.4195 (Mumford, Phillips, *J. Chem. Soc.* **1950**, 75). Insol in water. Refluxing with 10% aq NaOH decomposes 1-chlorohexane to 1-hexanol.

2197. α-Chlorohydrin. *3-Chloro-1,2-propanediol;* 3-chloro-1,2-dihydroxypropane; α-monochlorohydrin; β,β'-dihydroxyisopropyl chloride; glycerol α-monochlorohydrin; 3-chloropropylene glycol; Epibloc. $C_3H_7ClO_2$; mol wt 110.54. C 32.60%, H 6.38%, Cl 32.07%, O 28.95%. $CH_2ClCHOHCH_2OH$. Prepd from glycerol and HCl gas: Conant, Quayle, *Org. Syn.* **coll. vol. I**, 294 (1941). Toxicity study: C. H. Hine *et al., Arch. Ind. Health* **14**, 250 (1956).

Liquid. Sweetish taste. Tendency to turn straw color. d_4^{20} 1.3218. n_D^{20} 1.4831. bp_{760} 213° (dec); bp_{14} 114-120°; bp_{11} 115-117°. Sol in water, alcohol, ether. LD_{50} in mice, rats (g/kg): 0.16, 0.15 orally (Hine).

USE: To lower the freezing point of dynamite; in the manuf of dye intermediates. As rodent chemosterilant.

2198. Chloromethyl Methyl Ether. *Chloromethoxymethane;* methyl chloromethyl ether; monochloromethyl ether; chlorodimethyl ether; CMME. C_2H_5ClO; mol wt 80.51. C 29.84%, H 6.26%, Cl 44.03%, O 19.87%. CH_3OCH_2Cl. Prepd by passing HCl through a mixture of formalin and methanol: C. S. Marvel, P. K. Porter, *Org. Syn.* **coll. vol. I**, 377 (1941). *See also Beilstein* **1**, 580 (1918) and supplements. Commercial product usually contaminated by *sym*-dichloromethyl ether, *q.v.* Review of carcinogenic risk: *IARC Monographs* **4**, 239-245 (1974).

Colorless liquid, bp 59°. d_4^{20} 1.0605. n_D^{20} 1.39737.

Caution: Potential symptoms of overexposure are irritation of eyes, skin and mucous membranes; pulmonary edema, pulmonary congestion and pneumonia; burns, necrosis; coughing, wheezing; blood stained sputum; weight loss; bronchial secretions. *See NIOSH Pocket Guide to Chemical Hazards* (DHHS/NIOSH 90-117, 1990) p 68. The technical grade has been listed as a known carcinogen: *Seventh Annual Report on Carcinogens* (PB95-109781, 1994) p 40.

USE: In synthesis of chloromethylated compounds.

2199. 1-Chloro-2-methyl-1-propene. α-Chloroisobutylene; β,β-dimethylvinyl chloride; isocrotyl chloride; 2-meth-

Fujino *et al.*, Ger. pat. **2,321,174;** *eidem*, U.S. pat. **3,853,837** (1973, 1974 both to Takeda); S. Shinagawa, M. Fujino, *Chem. Pharm. Bull.* **23,** 229 (1975); *see also:* M. Fujino *et al., Biochem. Biophys. Res. Commun.* **49,** 863 (1972). Enzyme immunoassay in bovine plasma: J. Okada, S. Kondo, *ibid.* **33,** 4464 (1985). Field trial in bovine cystic ovarian disease: T. Nakao *et al., Japan. J. Vet. Sci.* **45,** 269 (1983); in induction of ovulation: T. Nakao *et al., Theriogenology* **20,** 111 (1983); D. A. Coleman *et al., ibid.* **30,** 149 (1988).

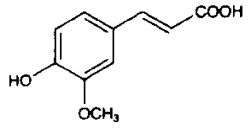
5-oxoPro–His–Trp–Ser–Tyr–Gly–Leu–Arg–ProNHCH$_2$CH$_3$

Monoacetate, $C_{55}H_{76}N_{16}O_{12}.C_2H_4O_2$, *U-69689E, Conceral, Ovalyse.*

Monoacetate pentahydrate, white, fluffy powder, $[\alpha]_D^{25}$ – 53.6° (c = 0.5 in 5% acetic acid).

THERAP CAT (VET): Gonad stimulating principle.

4110. Ferulic Acid. *3-(4-Hydroxy-3-methoxyphenyl)-2-propenoic acid; 4-hydroxy-3-methoxycinnamic acid;* 3-methoxy-4-hydroxycinnamic acid; caffeic acid 3-methyl ether. $C_{10}H_{10}O_4$; mol wt 194.19. C 61.85%, H 5.19%, O 32.96%. Widely distributed in small amounts in plants. Isoln from *Ferula foetida* Reg. *Umbelliferae:* H. Hlasiwetz, L. Barth, *Ann.* **138,** 61 (1866); from *Pinus laricio* Poir. *Abietineae:* M. Bamberger, *Monatsh.* **12,** 441 (1891); *see also Beilstein* **10,** 436 (1927) and supplements. Prepd by the interaction of vanillin, malonic acid and piperidine in pyridine for 3 weeks, then precipitating with HCl: Vorsatz, *J. Prakt. Chem.* **145,** 265 (1936); Pearl, Beyer, *J. Org. Chem.* **16,** 216 (1951). Sepn of *cis* and *trans* isomers: Comte *et al., Compt. Rend.* **245,** 1144 (1957). ^{13}C NMR study: C. J. Kelley *et al., J. Org. Chem.* **41,** 449 (1976). Discovery as a component of cell walls in wheat and barley: M. G. Smart, T. P. O'Brien, *Aust. J. Plant Physiol.* **6,** 485 (1979). Use as food preservative: T. Tsuchiya, M. Takasawa, **Japan. Kokai 75 18621** (1975 to Kyokuto Shibosan), *C.A.* **83,** 7602v (1975).



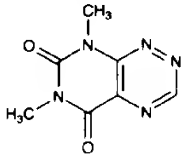
trans - Ferulic Acid

cis-Form, yellow oil. uv max (alcohol): 316 nm.

trans-Form, orthorhombic needles from water, mp 174°. uv max (alcohol): 236, 322 nm. Sol in hot water, alcohol, ethyl acetate. Moderately sol in ether. Sparingly sol in petr ether, benzene. Forms a sodium salt.

USE: Food preservative.

4111. Fervenulin. *6,8-Dimethylpyrimido[5,4-e]-1,2,4-triazine-5,7-(6H,8H)-dione;* 6,8-dimethyl-5,7-dioxo-5,6,7,8-tetrahydropyrimido[5,4-*e*]-*as*-triazine; 1,3-dimethylazalumazine; planomycin. $C_7H_7N_5O_2$; mol wt 193.17. C 43.53%, H 3.65%, N 36.26%, O 16.57%. Antibiotic from culture filtrates of *Streptomyces fervens:* Eble *et al., Antibiot. Ann.* **1959-1960,** 227. Structure: Daves *et al., J. Org. Chem.* **26,** 5256 (1961). Synthesis: Pfleiderer, Schündehütte, *Ann.* **615,** 42 (1958); Daves *et al., J. Am. Chem. Soc.* **84,** 1724 (1962); Yoneda, Nagamatsu, *Bull. Chem. Soc. Japan* **48,** 2884 (1975); Taylor, Sowinski, *J. Org. Chem.* **40,** 2321 (1975); S. Senda *et al., J. Am. Chem. Soc.* **99,** 7358 (1977).

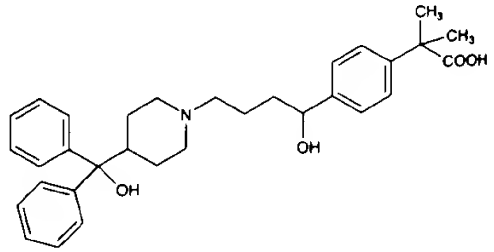


Yellow orthorhombic crystals, mp 178-179°. uv max (ethanol): 238, 275, 340 nm (ε 18,500, 1600, 4200). Sol in practically all of the common organic solvents; sol in cold water to about 2 mg/ml; in hot water to about 40 mg/ml. Practically insol in hydrocarbons. Labile to alkali; stable to acid.

4-Oxide, $C_7H_7N_5O_3$. Synthesis: M. Ichiba *et al., J. Heterocycl. Chem.* **14,** 175 (1977); K. Senga *et al., Heterocycles* **6,** 273 (1977); synthesis and conversion to fervenulin: M. Ichiba *et al., J. Org. Chem.* **43,** 469 (1978). Crystals from alc, mp 179-180°. uv max (alc): 240, 304 nm (log ε 4.10, 3.21).

4112. Feverfew. Featherfew; featherfoil; midsummer daisy. *Tanacetum parthenium* (L.) Sch. Bip., (formerly *Chrysanthemum parthenium* (L.) Bernh.) *Compositae,* a perennial, strongly aromatic herb found in Britain and the Balkan peninsula. Used medicinally since the Middle Ages as a febrifuge. Constituents include sesquiterpene lactones such as parthenolide, *q.v.:* P. J. Hylands, D. M. Hylands in *Development of Drugs and Modern Medicines,* J. W. Gorrod *et al.,* Eds. (Ellis Horwood, Chichester, 1986) pp 100-104. Inhibition of prostaglandin biosynthesis by feverfew extract: H. O. J. Collier *et al., Lancet* **2,** 922 (1980). Effect on human platelet phospholipase: A. N. Makheja, J. M. Bailey, *ibid.* 1054 (1981); *eidem, Prostaglandins, Leukotrienes Med.* **8,** 653 (1982); J. K. Thakkar *et al., Biochim. Biophys. Acta* **750,** 134 (1983). Inhibition of platelet secretory activity: S. Heptinstall *et al., Lancet* **1,** 1071 (1985); S. Heptinstall *et al., J. Pharm. Pharmacol.* **39,** 459 (1987). Structure and anti-secretory activity study: W. A. Groenewegen *et al., ibid.* **38,** 709 (1986). Clinical trials in migraine using freeze dried feverfew leaves: E. S. Johnson *et al., Brit. Med. J.* **291,** 569 (1985). Use of oil extract in migraine: E. S. Johnson *et al.,* U.S. pat. **4,758,433** (1988 to R. P. Scherer). *Review:* M. I. Berry, *Pharm. J.* **232,** 611-614 (1984). Brief review of activity and possible side effects: C. A. Baldwin *et al., ibid.* **239,** 237-238 (1987).

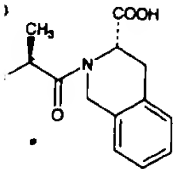
4113. Fexofenadine. *α,α-Dimethyl-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]benzeneacetic acid;* carboxyterfenadine; terfenadine carboxylate; MDL-16455; Allegra. $C_{32}H_{39}NO_4$; mol wt 501.67. C 76.62%, H 7.84%, N 2.79%, O 12.76%. Identification as a metabolite of terfenadine, *q.v.*, and antihistaminic activity: D. A. Garteiz *et al., Arzneimittel-Forsch.* **32,** 1185 (1982). HPLC separation from terfenadine: K. Y. Chan *et al., J. Chromatog.* **571,** 291 (1991); determn in biological fluids: A. Terhechte, G. Blaschke, *ibid. (A)* **694,** 219 (1995). Effects on cardiac K$^+$ channels: D. Rampe *et al., Mol. Pharmacol.* **44,** 1240 (1993). Synthesis: S. H. Kawai *et al., J. Org. Chem.* **59,** 2620 (1994). Use as antihistaminic: B. E. McNutt, **PCT Int.** pat. **Appl. 95 10278** (1995 to Marion Merrell Dow).



White crystals from methanol, mp 142°-143°.

THERAP CAT: Antihistaminic.

4114. Fialuridine. *1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodo-2,4(1H,3H)-pyrimidinedione;* 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodouracil; 5-iodo-2'-fluoroarauracil; FIAU. $C_9H_{10}FIN_2O_5$; mol wt 372.09. C 29.05%, H 2.71%, F 5.11%, I 34.11%, N 7.53%, O 21.50%. Exptl antiviral agent; nucleoside analog with antihepatitis B activity. Prepn: K. A. Watanabe *et al., J. Med. Chem.* **22,** 21 (1979). Antiviral activity: J. M. Colacino, C. Lopez, *Antimicrob. Ag. Chemother.* **24,** 505 (1983); K. A. Staschke *et al., Antivir. Res.* **23,** 45 (1994). Clinical pharmacokinetics: R. R. Bowsher *et al., Antimicrob. Ag. Chemother.* **38,** 2134 (1994). Report of trial suspension: S. R. Ahmed, *Lancet* **342,** 166 (1993). Evaluation of mechanism of hepatotoxicity: L. Cui *et al., J. Clin. Invest.* **95,** 555 (1995). Clinical

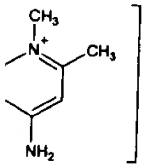


.HCl, *'CI-906, PD-109452-2, equin, Acuitel, Korec, Quina-* e-toluene, mp 120-130°. $[\alpha]_D^{23}$ Klutchko). Also reported as acetonitrile, mp 119-121.5°. ol) (Goel, Krolls). LD_{50} in g): 1739, 1840, 4280, 3541 Kaplan, 1989).
ilat, CI-928. Hydrate, crys-, mp 166-168°. $[\alpha]_D^{23}$ +20.9°

iiazide, *Accuretic, Acequide,*

e.

*'-Amino-6-[(2-amino-1,6-di-amino]-1,2-dimethylquinoli-*ino-6-[(2-amino-6-methyl-4-iinaldinium methosalts; 4-1-4-pyrimidinyl)amino]-1,2-no-6-(2-amino-6-methyl-4-dimethosalts; M-7555; An-D. G. Davey, *Brit. J. Phar-*S. pat. **2,585,917** (1952 to *oc.* **1953,** 59.



, creamy white crystals Freely sol in water. LD_{50} , Davey).
mp 312-313° (dec). Spar-

mp 316-317° (dec). Spar-iice: 10-15 mg/kg (Curd,

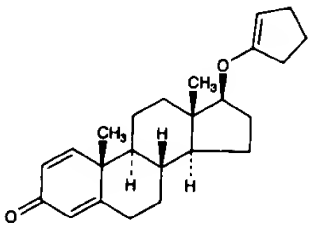
ypanosoma).

:odiazine; benzo[*a*]pyrimi-iiazine. $C_8H_6N_2$; mol wt 21.52%. Prepn from 2-Riedel, Ger. pat. **174,941;** *dl.* **8,** 1238; Bogert, Mc-) (1927).

:N

quinoline. Slightly bitter $^{D}p_{764}$ 241.5°. Freely sol in any organic solvents.

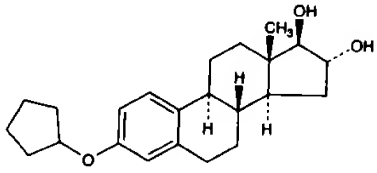
*l-Cyclopenten-1-yloxy)an-*stosterone 17-cyclopent-$C_{24}H_{32}O_3$; mol wt 352.52. pn from 17β-hydroxyan-*Chem. & Ind. (London)*



Crystals from ethanol, mp 133-135°. $[\alpha]_D^{20}$ +61° (dioxane). uv max: 244-245 nm ($E_{1cm}^{1\%}$ 430-450). Practically insol in water. Sol in many organic solvents; sparingly sol in ethanol, hexane. Soly in sesame oil: 40-45 mg/ml.
THERAP CAT: Anabolic.

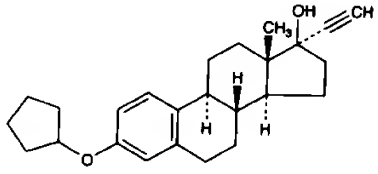
8237. Quince Seed. Gum quince seed; semen cydonia; golden apple seed; cydonia seed. Seed of *Cydonia oblonga* Mill. (*C. vulgaris* Pers.), *Rosaceae. Habit.* Southern Asia, Europe; widely cultivated. *Constit.* Amygdalin, emulsin, about 15% fatty oil, about 20% of a mucilage named cydonin. Brief review of seed and gum uses: BeMiller in *Industrial Gums,* R. L. Whistler, Ed. (Academic Press, New York, 2nd ed., 1973) pp 339-345.
USE: Gum from the seeds as suspending agent, stabilizer; in hair and cosmetic prepns.

8238. Quinestradiol. *(16α,17β)-3-(Cyclopentyloxy)estra-1,3,5(10)-trien-16,17-diol;* quinestradol; estriol 3-cyclopentyl ether; Colpovis; Pentovis. $C_{23}H_{32}O_3$; mol wt 356.51. C 77.49%, H 9.05%, O 13.46%. Prepn from estriol and cyclopentylbromide: Ercoli, **Brit. pat. 909,662** (1962 to Vismara).



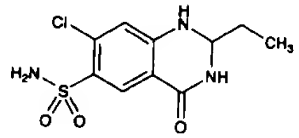
Crystals, mp 98-100°.
THERAP CAT: Estrogen.

8239. Quinestrol. *(17α)-3-(Cyclopentyloxy)-19-norpregna-1,3,5(10)-trien-20-yn-17-ol;* 17α-ethinylestradiol 3-cyclopentyl ether; W-3566; Estrovis. $C_{25}H_{32}O_2$; mol wt 364.53. C 82.37%, H 8.85%, O 8.78%. Prepn: Ercoli, Gardi, *Chem. & Ind. (London)* **1961,** 1037; Ercoli, U.S. pat. **3,159,543;** Ercoli *et al.,* U.S. pat. **3,231,567** (1964, 1966, both to Vismara).



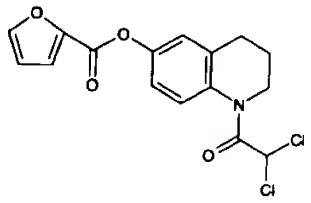
Crystals, mp 107-108°. $[\alpha]_D^{25}$ +5° (c = 0.5 in dioxane).
THERAP CAT: Estrogen.

8240. Quinethazone. *7-Chloro-2-ethyl-1,2,3,4-tetrahydro-4-oxo-6-quinazolinesulfonamide;* 7-chloro-2-ethyl-6-sulfamoyl-1,2,3,4-tetrahydro-4-quinazolinone; 7-chloro-2-ethyl-1,2,3,4-tetrahydro-4-oxo-6-sulfamoylquinazoline; CL-36010; Hydromox; Aquamox. $C_{10}H_{12}ClN_3O_3S$; mol wt 289.74. C 41.45%, H 4.17%, Cl 12.24%, N 14.50%, O 16.57%, S 11.07%. Prepn: Cohen *et al., J. Am. Chem. Soc.* **82,** 2731 (1960); Cohen, Vaughan, Jr., U.S. pat. **2,976,289** (1961 to Am. Cyanamid).



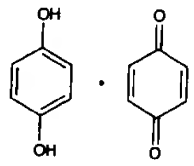
Fibrous crystals from 50% acetone, mp 250-252°. Sol in acetone, alcohol.
THERAP CAT: Diuretic, antihypertensive.

8241. Quinfamide. *2-Furancarboxylic acid 1-(dichloroacetyl)-1,2,3,4-tetrahydro-6-quinolinyl ester;* 2-furoic acid ester with 1-(dichloroacetyl)-1,2,3,4-tetrahydro-6-quinolinol; 1-(dichloroacetyl)-6-(2-furoyloxy)-1,2,3,4-tetrahydroquinoline; Win-40014; Amenox; Amenide. $C_{16}H_{13}Cl_2NO_4$; mol wt 354.19. C 54.26%, H 3.70%, Cl 20.02%, N 3.95%, O 18.07%. Prepn: D. M. Bailey, U.S. pat. **3,997,542** (1976 to Sterling); D. M. Bailey *et al., J. Med. Chem.* **22,** 600 (1979). Amebicidal activity and toxicological evaluation: R. G. Slighter *et al., Parasitology* **81,** 157 (1980). Distribution and metabolism in rats: J. F. Baker, *Arch. Int. Pharmacodyn.* **258,** 29 (1982). Clinical evaluation in adults with chronic amebiasis: L. Guevara *et al., Clin. Therap.* **6,** 43 (1983); in children: F. A. Rojas *et al., ibid.* 47.



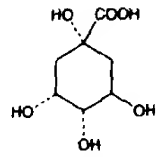
Crystals from ethyl acetate, mp 150.5-151°.
THERAP CAT: Antiamebic.

8242. Quinhydrone. *2,5-Cyclohexadiene-1,4-dione compd with 1,4-benzenediol (1:1);* green hydroquinone. $C_{12}H_{10}O_4$; mol wt 218.21. C 66.05%, H 4.62%, O 29.33%. An addn compd of one mol hydroquinone and one mol quinone. Prepn from hydroquinone and quinone: Gattermann-Wieland, *Praxis des Organischen Chemikers* (de Gruyter, Berlin, 40th ed., 1961) p 270. Alternate prepn by the action of ferric ammonium sulfate on hydroquinone: A. I. Vogel, *Practical Organic Chemistry,* (Longmans, London, 3rd ed., 1959) p 747. Toxicity study: Woodward *et al., Fed. Proc.* **8,** 348 (1949).



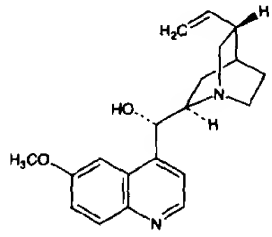
Green crystals with metallic luster; reddish-brown by transmitted light. d 1.40. mp 171°; sublimes with partial decompn. Slightly sol in cold water; sol in hot water, ammonia, alc, ether. Insol in petr ether. LD_{50} orally in rats: 225 mg/kg (Woodward).
USE: In pH determinations (quinhydrone electrode).

8243. Quinic Acid. *[1R-(1α,3α,4α,5β)]-1,3,4,5-Tetrahydroxycyclohexanecarboxylic acid;* chinic acid; kinic acid; hexahydro-1,3,4,5-tetrahydroxybenzoic acid. $C_7H_{12}O_6$; mol wt 192.17. C 43.75%, H 6.29%, O 49.95%. Found in cinchona bark, particularly in South American barks; also in many other plants, such as tobacco leaves, carrot leaves, apples, peaches, pears, plums, etc. Structure and configuration: Fischer, Dangschat, *Ber.* **65,** 1009 (1932). Total synthesis: Grewe *et al., ibid.* **87,** 793 (1954); Smissman, Oxman, *J. Am. Chem. Soc.* **85,** 2184 (1963). Stereospecific synthesis: Wolinsky *et al., J. Org. Chem.* **29,** 3596 (1964). *Review:* Bohm, *Chem. Rev.* **65,** 435 (1965).



White crystals; strong acid taste. d 1.64. mp 162-163°; at higher temps forms a lactone. $[\alpha]_D^{20}$ −42° to −44° in water. Sol in 2.5 parts water, in alcohol, glacial acetic acid.

8244. Quinidine. *(9S)-6′-Methoxycinchonan-9-ol; α-(6-methoxy-4-quinolyl)-5-vinyl-2-quinuclidinemethanol;* conquinine; pitayine; β-quinine. $C_{20}H_{24}N_2O_2$; mol wt 324.42. C 74.05%, H 7.46%, N 8.63%, O 9.86%. A dextrorotatory stereoisomer of quinine, *q.v.* Present in cinchona barks to the extent of 0.25-3.0%. Found in quinine sulfate mother liquors. Review of structural elucidation and early synthetic studies: R. B. Turner, R. B. Woodward, in *The Alkaloids,* **vol. 3,** 1-63 (1953). Configuration: Prelog, Zalán, *Helv. Chim. Acta* **27,** 535 (1944); Prelog, Häfliger, *ibid.* **33,** 2021 (1950); Roth, *Pharmazie* **16,** 257 (1961). Crystal and molecular structure: R. Doherty *et al., J. Pharm. Sci.* **67,** 1698 (1978). Rotatory dispersion studies: Lyle, Gaffield, *Tetrahedron Letters* **1963,** 1371. Prepn by isomerization of quinine: W. E. Doering *et al., J. Am. Chem. Soc.* **69,** 1700 (1949). Total synthesis: J. Gutzwiller, M. Uskokovic, *ibid.* **92,** 204 (1970); *eidem, Helv. Chim. Acta* **56,** 1494 (1973); *eidem, J. Am. Chem. Soc.* **100,** 576 (1978). Toxicity data: C. Turba *et al., Arzneimittel-Forsch.* **18,** 1127 (1968); K. Dietmann *et al., ibid.* **27,** 589 (1977). Comprehensive description of the sulfate: M. A. Loutfy *et al., Anal. Profiles Drug Subs.* **12,** 483-546 (1983). Clinical evaluation in severe malaria: R. E. Phillips *et al., N. Engl. J. Med.* **312,** 1273 (1985). Review of pharmacology and clinical efficacy in cardiac arrhythmias: J. W. Mason, L. M. Hondeghem, *Ann. N.Y. Acad. Sci.* **432,** 162-176 (1984); A. R. Leon, J. D. Merlino, *Heart Dis. Stroke,* **2,** 407-413 (1993).



Triboluminescent. mp 174-175° after drying of solvated crystals. $[\alpha]_D^{15}$ +230° (c = 1.8 in chloroform), $[\alpha]_D^{17}$ +258° (alc), $[\alpha]_D^{17}$ +322° (c = 1.6 in 2*M* HCl). pK_1 (20°) 5.4; pK_2 10.0. Blue fluorescence in dil H_2SO_4. The uv absorption spectrum is identical with that of quinine. One gram dissolves in about 2000 ml cold, 800 ml boiling water, 36 ml alcohol, 56 ml ether, 1.6 ml chloroform; very sol in methanol. Practically insol in petr ether. LD_{50} in rats (mg/kg): 30 i.v., 263 orally (Dietmann).

Hemipentahydrate, prisms from dil alcohol, loses ½ H_2O in air, mp ~168°.

Hydrogen sulfate tetrahydrate, $C_{20}H_{24}N_2O_2 \cdot H_2SO_4 \cdot 4H_2O$, ***quinidine bisulfate, Chinidin-Duriles, Kiditard, Kinichron, Kinidin Durules, Quiniduran.*** Rods, sol in 8 parts water with blue fluorescence.

Sulfate dihydrate, $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$, ***Cin-Quin, Quinidex Extentabs, Quinicardine, Quinora.*** White, very bitter, odorless, fine crystals, frequently cohering in masses. Darkens on exposure to light. Does not lose all of its water below 120°. $[\alpha]_D^{25}$ ~+212° (95% alcohol); ~+260° (dil HCl). pKa 4.2, 8.8. pH (1% aq soln): 6.0-6.8. One gram dissolves in about 90 ml water, 15 ml boiling water, 10 ml alcohol, 3 ml methanol, 12 ml chloroform. Insol in ether, benzene. *Protect from light.* LD_{50} in mice, rats (mg/kg): 700, 455.8 orally; 83, 56 i.v. (Turba).

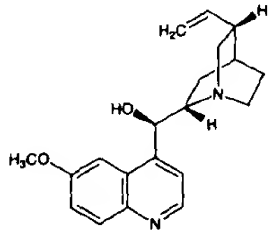
Gluconate, $C_{26}H_{34}N_2O_9$, ***gluconic acid quinidine salt, Duraquin, Quinaglute.*** Crystals, mp 175-176.5°. Sol in 9 parts water, 60 parts alcohol.

Polygalacturonate, ***Cardioquin, Galactoquin, Naticardina.*** $(C_{20}H_{24}N_2O_2 \cdot C_6H_{10}O_7 \cdot H_2O)_x$. Prepn: A. Halpern *et al., Am. J. Pharm.* **130,** 190 (1958). Pharmacology: A. Halpern *et al., Antibiot. Chemother.* **9,** 97 (1959). Amorphous powder, mp 180° (dec). Anhydr product is insol in methanol, ethanol, chloroform, ether, acetone, dioxane. Soly in hot 40% methanol or ethanol: 12%; in water at 25°: ~2%. LD_{50} in rats, mice (mg/kg): 3200 ± 350, 2680 ± 210 orally (Halpern, 1959).

THERAP CAT: Antiarrhythmic (class IA); antimalarial.

THERAP CAT (VET): Antiarrhythmic.

8245. Quinine. *(8α,9R)-6′-Methoxycinchonan-9-ol.* $C_{20}H_{24}N_2O_2$; mol wt 324.42. C 74.05%, H 7.46%, N 8.63%, O 9.86%. Primary alkaloid of various species of *Cinchona* (Rubiaceae), *see* Cinchona. Representative samples of dried bark contain ~0.8 to 4% quinine. Optical isomer of quinidine, *q.v.* Isoln: Pelletier, Caventau, *Ann. Chem. Phys.* [2], **15,** 291 (1820). Extraction procedure: Jucker, Stoll, in *Ullmann's Enzyklopädie der technischen Chemie* **3,** 213-218 (1953). Configuration: Prelog, Zalán, *Helv. Chim. Acta* **27,** 535 (1944); Prelog, Häfliger, *ibid.* **33,** 2021 (1950); Roth, *Pharmazie* **16,** 257 (1961). Synthesis: Woodward, Doering, *J. Am. Chem. Soc.* **66,** 849 (1944); **67,** 860 (1945); Taylor, Martin, *ibid.* **94,** 6218 (1972); Gutzwiller, Uskokovic, *ibid.* **100,** 576 (1978); G. Grethe *et al., ibid.* 589; T. Imanishi *et al., Chem. Pharm. Bull.* **30,** 1925 (1982). Review of structural elucidation and early synthetic studies: R. B. Turner, R. B. Woodward in *The Alkaloids,* **vol. 3,** 1-63 (1953); of bioactivity: F. E. Hahn, Ed. in *Antibiotics* **vol. 5**(pt. 2) (Springer-Verlag, New York, 1979) pp 353-362. Comprehensive description of the hydrochloride: F. J. Muhtadi *et al., Anal. Profiles Drug Subs.* **12,** 547-621 (1983). LC determn in soft drinks: L. P. Valenti, *J. Assoc. Off. Anal. Chem.* **68,** 782 (1985). HPLC determn in blood: V. K. Dua *et al. J. Chromatog.* **614,** 87 (1993). Clinical evaluation to relieve nocturnal leg cramps: P. S. Connolly *et al., Arch. Intern Med.* **152,** 1877 (1992). Clinical efficacy in malaria: P. G. Kremsner *et al., J. Infect. Dis.* **169,** 467-470 (1994).



Triboluminescent, orthorhombic needles from abs alcohol, mp 177° (some decompn). Sublimes in high vacuum at 170-180°. $[\alpha]_D^{15}$ −169° (c = 2 in 97% alcohol), $[\alpha]_D^{17}$ −117° (c = 1.5 in chloroform), $[\alpha]_D^{15}$ −285° (c = 0.4*M* in 0.1*N* H_2SO_4). pK_1 (18°) 5.07; pK_2 9.7. pH of satd aq soln 8.8. Absorption spectra: Dobbie, Lauder, *J. Chem. Soc.* **99,** 1260 (1911); Dobbie, Fox, *ibid.* **101,** 78 (1912). Fluorescence: Rabe, Marschall, *Ann.* **382,** 362 (1911). The blue fluorescence is especially strong in dil H_2SO_4. One gram dissolves in 1900 ml water, 760 ml boiling water, 0.8 ml alcohol, 80 ml benzene (in 18 ml benzene at 50°), in 1.2 ml chloroform; 250 ml dry ether, 20 ml glycerol, 1900 ml of 10% ammonia water. Almost insol in petr ether.

Trihydrate, microcrystalline powder, mp 57°, efflorescent, loses one H_2O in air, two H_2O over H_2SO_4, anhydr at 125°.

Bisulfate heptahydrate, $C_{20}H_{24}N_2O_2 \cdot H_2SO_4 \cdot 7H_2O$, ***Biquinate, Dentojel, Quinbisan.*** Very bitter crystals or cryst powder; efflorescent on exposure to air and darkens on exposure to light. One gram dissolves in 9 ml water, 0.7 ml boiling water, 23 ml alcohol, 0.7 ml alcohol at 60°, 625 ml chloroform, 2500 ml ether, 15 ml glycerol. pH: 3.5.

Dihydrochloride, $C_{20}H_{24}N_2O_2 \cdot 2HCl$, ***quinine dichloride, quinine bimuriate, acid quinine hydrochloride.*** Very bitter powder or crystals. One gram dissolves in about 0.6 ml